IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Samn Raffaniello | Atty Dkt: 2098.002A

Serial No.: 10/829,143 | Group Art Unit: 1651

Filed: April 21, 2004 | Examiner: Ware, Deborah K.

Title: ANCROD IRRADIATED, IMPREGNATED OR COATED SUTURES AND OTHER FIRST AID OR WOUND MANAGEMENT BANDAGING MATERIALS FOR MINIMIZING SCARRING AND/OR PREVENTING EXCESSIVE SCAR FORMATION

DECLARATION UNDER 37 CFR §1.132

I, Gregory John Del Zoppo, a citizen of the United States of America, declare that:

1. I hold undergraduate and graduate degrees from the following institutions: B.S. Chemistry, University of Washington, Seattle, Washington; M.S., Biology (Molecular Biology, Neurophysiology), California Institute of Technology, Pasadena, California; M.D., University of Washington School of Medicine, Seattle, Washington.

2. Subsequent to obtaining my medical degree, I completed externship, internship and residency programs at The National Hospital, Institute of Neurology, Queen Square, London, WC1N 3BG, UK; Internal Medicine, St. Louis University Affiliated Hospitals, St. Louis, Missouri; and Internal Medicine, University of Oregon Health Sciences Center, Portland, Oregon, respectively. Additionally, I served as a Senior House Officer and Registrar (Locum), Neurology, The National Hospital, Institute of Neurology, Squeen Square, London, WC1N 3BG, U.K. I served a fellowship, in Clinical Hematology/Medical Oncology at the University of Oregon Health Sciences Center, Portland, Oregon.

3. I am licensed to practice medicine by the States of California, Oregon, Washington and in the United Kingdom, and I am certified by the American Board of Internal Medicine in Internal Medicine and Hematology.

4. I have been employed since 1982 as follows: by the Scripps Clinic and Research Foundation as, sequentially, a Senior Research Associate, a Member of the Division of Hematology/Medical Oncology, an Assistant Member of the Department of Basic and Clinical Research/Molecular and Medicine, Director of the Coagulation Laboratory, Department of Clinical Pathology and an Associate Professor in the Department of Molecular and Experimental Medicine. Currently, I am a Professor in the Department of Medicine, Division of Hematology and an Adjunct Professor in the Department of Neurology, University of Washington, Seattle, Washington. Also, I am on the Advisory Board at Boehringer Ingelheim Pharmaceuticals, with headquarters in Ingelheim, Germany and Richfield, Connecticut; the Scientific Advisory Board, Bio-Seek, Inc., in Burlingame, California; NTI, Edgewater, New Jersey; Remedy Pharmaceuticals in New York; and, Lundbeck, Copenhagen, Denmark for specific projects.

5. I am a member of the following professional organizations:
   - Fellow, Council on Stroke; American Heart Association/American Stroke Association
   - Fellow, Council on Arteriosclerosis, Thrombosis, and Vascular Biology, American Heart Association
   - Society for Neuroscience
   - International Society of Thrombosis and Haemostasis
   - International Society of Cerebral Blood Flow and Metabolism
   - American Neurological Association
   - International Stroke Society/World Stroke Organization
   - American Society of Hematology
   - American College of Physicians
   - American Association for the Advancement of Science
   - Molecular Medicine Society
   - New York Academy of Sciences

6. I have been a recipient of the following research support:

1983-1987 **PO1 HL31950,** Part III (Program Project) of the NHLBI, NIH:
Antithrombotic (including thrombolytic) interventions in experimental stroke

1986 - 1987 **Nr. Aa 2/75-1** of the DFG:
Thrombolytic therapy in acute thrombotic stroke

1988 - 2006 **RO1 NS26945** of the NINDS, NIH:
Microvessel Occlusion Formation in Focal Cerebral Ischemia (inflammation and microvascular "no-reflow"
+ ***Supplement***: Behavioral outcomes

1992 - 1993 **Upjohn Pharmaceuticals:**
Effects of tirilazad mesylate on outcome in experimental focal cerebral ischemia

1994 - 1999 **Telios Pharmaceuticals, Inc.:**
Effects of the platelet GPIIb/IIIa (integrin $\alpha_{IIb}\beta_3$) inhibitor TP9201 on microvascular patency

1992 - 2006 **RO1 NS26945** of the NINDS, NIH:
Microvessel Occlusion Formation in Focal Cerebral Ischemia (microvessel integrin-matrix interactions in focal cerebral ischemia)
+ ***Supplement***: Equipment for computerized video-imaging

1999 - 2004 **RO1 NS38710** of the NINDS, NIH:
Metalloproteinases and Neurons in Focal Ischemia
+ ***Supplement***: Microarray collaboration with Novartis-GNF

2004 - Present **Javits Neuroscience Investigator Award**
R37 NS38710 of the NINDS, NIH
Metalloproteinases and Neurons in Focal Ischemia (non-MMP vascular matrix proteases and their impact on neuron function)

2005 - Present **RO1 NS053715** of the NINDS, NIH:
Neurovascular Adhesion Receptors and Barrier Integrity

2006 - Present **R37 NS38710** of the NINDS, NIH
Metalloproteinases and Neurons in Focal Ischemia
+ ***Supplement***: Consortium-building supplement

7. In addition, I have been responsible for the following clinical investigations:

1984 - 1987 Organizer and Principal Investigator, Two-site prospective study of: Thrombolysis in acute thrombotic and thromboembolic stroke, together with Abteilung Neurologie, Klinikum RWTH (University of Aachen), Aachen, Federal Republic of Germany

1987 - 1990 Organizer and Principal Investigator, Multicenter international prospective study: An Open Study of the Safety and Efficacy of Various Doses of rt-PA in Patients with Acute Thrombotic Stroke.

1990 - 1992 Organizer, Principal Investigator, and Chairman, Steering Committee, Multicenter international study: Thrombolytic Therapy in Acute Thrombotic/Thromboembolic Stroke (TTATTS).

1992 - 1994 Member, Safety and Ethics Committee, Multicentre European prospective study: European Cooperative Acute Stroke Study (ECASS).

1993 - 1995 Organizer, Principal Investigator, and Chairman of Executive/Steering Committee, Multicentre North American Study: Pro-urokinase in Acute Cerebral Thromboembolism (PROACT).

1996 - 1998 Member, Safety and Ethics Committee, Multicentre European prospective study: European Cooperative Acute Stroke Study (ECASS) - II.

1997 - 1998 Member, Executive Committee, Carotid Artery Stenting *vs.* Endarterectomy Trial (CASET).

1997 - 2000 Member, Executive Committee of phase II and phase III Multicenter prospective studies, Hu23F2G Anti-adhesion to Limit cytoToxic injury in Stroke (HALTS) Study.

1999 - 2004 Member, Steering Committee, IL-1ra in Acute Ischemic Stroke Study, University of Manchester, Manchester, U.K.

2007 – Present Principal Investigator, Ancrod Stroke Program I (ASP I) Phase III study of Viprinex for Emergency Stroke, Neurobiological Technologies, Inc.

2002 - 2007 Member, Data Safety and Monitoring Board (DSMB); Hypopituitarism after Moderate and Severe Head Injury, (Daniel F. Kelly, Principal Investigator), R01 NS40777-OH12 (NINDS).

2002 - Present Chairman, (DSMB); Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF), (Shunichi Homma/Patrick Pullicino, Principal Investigator), U01 NS39143 and U01 NS43975 (NINDS).

2005 - Present Member, (DSMB); Ceftriaxone in Amyotrophic Lateral Sclerosis (ALS), (Merit E. Cudkowicz, Principal Investigator) (NINDS).

2006 – Present Chairman, Advisory Board and Principal Investigator, ASP-I.

8. I currently serve on the editorial boards of *Stroke, Cerebrovascular Disease, and the Journal of Cerebral Blood Flow and Metabolism* and am the author of numerous publications, textbooks, chapters and presentations. Examples of my work include:

1. del Zoppo GJ, Zeumer H, Harker LA: Thrombolytic therapy in acute stroke: Possibilities and hazards. Stroke 17:595-607, 1986.

2. del Zoppo GJ: Antiplatelet therapy in TTP. Semin Hematol 24:130-139, 1987.

3. del Zoppo GJ. Thrombin. Maybe not so spellbinding. Neurology 14: 768-769, 2004.

4. del Zoppo GJ. Plasminogen activators and ischemic stroke. J Thromb Haemost 3: 1376-1378, 2005.

5. del Zoppo GJ, Kalafut, M. Mechanisms of thrombosis and thrombolysis. In: Stroke: Pathophysiology, Diagnosis and Management. Fourth Edition. Mohr JP, Choi DW, Grotta JC, Weir B, and Wolf PA (Eds) Blackwell Scientific (New York), pp. 785-798, 2004.

6. Hamann GF, del Zoppo GJ. Vascular biology of cerebral arteries and microvessel. In: Stroke: Pathophysiology, Diagnosis, and Management. Mohr JP, Choi DW, Grotta JC, Weir B, and Wolf PA (Eds) Blackwell Scientific (New York), pp. 775-783, 2004.

7. del Zoppo GJ, Mabuchi T, Koziol JA, Fukuda S, Eggleston LL. Vascular and Non-Vascular Matrix (ECM) degradation. In: Pharmacology of Cerebral Ischemia. Krieglstein J and Klumpp (Eds) MedPharm Scientific Publishers (Stuttgart), pp. 3-19, 2005.

8. del Zoppo GJ. Chapter 102. Prevention and treatment of acute stroke. In: Hemostasis and Thrombosis. Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber SZ (Eds) Lippincott Williams &Wilkins (Philadelphia), pp. 1477 - 1496, 2006.

9. del Zoppo GJ. Chapter 31. Antithrombotic approaches in cerebrovascular disease. In: Vascular Medicine. A Companion to Braunwalds Heart Disease. Creager MA, Dzau VJ, Loscalzo J (Eds) Saunders-Elsevier (Philadelphia), pp. 449 - 466, 2006.

10. del Zoppo GJ. Chapter 13. Vascular hemostasis and brain embolism. In: Brain Embolism. Caplan LR and Manning WJ (Eds) Informa Healthcare (New York), pp. 243-258, 2006.

11. del Zoppo GJ and Moskowitz MA. Translating interventions from ischemic stroke models to patients: The view in 2008. In: Clinical trials in Neurological Disease, Karger (In press) (2008)

9. I have read the claims of the above-identified U.S. patent application and the USPTO Office Action dated April 17, 2008 relative to the instant application including the Edwardson et al. reference cited in the Office Action. My understanding of the claimed invention is that it relates to a method for minimizing scarring at a wound site by administration of a defibrinogenation agent such as ancrod in an amount sufficient to minimize scarring. According to the Office Action, Edwardson et al. discloses the administration of ancrod to a wound site. In my opinion, based on a fair reading of Edwardson et al., one of skill in the art would not conclude that Edwardson et al. suggests the administration of ancrod to a wound site.

The present invention relates to a method for minimizing scarring at a wound site. Scarring is a by-product of the wound healing process, which is a complex series of events beginning with initiation of the coagulation cascade. Fibrinogen is cleaved by thrombin to generate fibrin, which promotes clotting and provides the structural framework for early phases of the healing process. This is the underlying principle of fibrin sealants, which are designed to mimic the initial clotting event.

Fibrinogen and fibrin are believed to play key roles in scar formation, making fibrin reduction a logical strategy for reducing or avoiding excess scarring. Fibrin formation by ancrod is fundamentally different from fibrin formation by thrombin in that the ancrod-generated fibrin is less stable; unlike thrombin, which cleaves both fibrinopeptides A and B from fibrinogen, ancrod cleaves only fibrinopeptide A. The result is a fibrin monomer that is markedly different than thrombin-generated fibrin, in that the ancrod-generated fibrin is soluble, not cross-linked and less resistant to degradation by plasmin. This provides the rationale for using ancrod to

reduce levels of fibrinogen and fibrin at the wound site, thereby avoiding excess scarring associated with fibrin deposition.

I have read the Edwardson et al. reference cited by the examiner. In my opinion, the Edwardson reference does not suggest the instant invention for the reasons cited below.

Edwardson et al. teaches a fibrin composition that can be applied to a wound site and will function as a fibrin sealant when contacted with the wound. The composition is purported to comprise any type of fibrin monomer, including soluble non-cross-linked fibrin (fibrin I), also for example, as generated by ancrod. Because it is not cross-linked, fibrin I differs from thrombin-formed cross-linked fibrin in its susceptibility to plasmin degradation and stability of the resultant clot. However, fibrin I can undergo further conversion to fibrin II when contacted with thrombin, for example, when blood or plasma is present at the wound site. For that condition, the action of thrombin to produce cross-linked fibrin is essential.

Edwardson et al. discloses that fibrin I (non-cross-linked fibrin) may be obtained from any source so long as the fibrin monomer can be converted to fibrin polymer or the non-crosslinked fibrin can be converted to cross-linked fibrin. According to Edwardson et al., fibrin from a whole blood source will retain sufficient quantities of prothrombin, factor XIII and other components of the coagulant cascade so that the non-cross-linked fibrin I can be converted to cross-linked fibrin II without the addition of exogenous thrombin and factor XIII. (col. 5, lines 9-24.)

Edwardson et al. further teaches that non-cross-linked fibrin I, which is obtained from exposure of fibrinogen to ancrod, is preferred because it can more readily, as compared to fibrinogen, be converted to cross-linked fibrin. According to Edwardson, if the non-cross-linked fibrin I comes in contact with blood, for example, on a wound, the patient's own thrombin and factor XIII may convert the fibrin I to cross-linked fibrin II.

A method for generating fibrin I monomer from a fibrinogen source using ancrod as the thrombin-like enzyme is disclosed at column 6, lines 25-35 of Edwardson et al. Beginning at col. 8, line 53, Edwardson provides a lengthy discussion of employing thrombin-like enzyme that

is immobilized on a solid support to convert fibrinogen to fibrin. This is done so the enzyme can be removed from the plasma following fibrin generation, thereby preventing the fibrin composition from being contaminated by the enzyme.

In my opinion, when the teachings of Edwardson et al. are viewed in their entirety in light of what is known in the art about coagulation in general and cleavage of fibrinogen by ancrod in particular, one of skill in the art would conclude that Edwardson et al. intended to make a fibrin preparation that is 1) easy to manipulate because of its solubility, but which 2) gives rise to a suitable fibrin sealant when contacted with blood at the wound site, because the non-cross-linked fibrin is readily converted to cross-linked fibrin at the wound site.

In my opinion, Edwardson et al. contains no suggestion that the preparation should include ancrod, nor does Edwardson indicate that administration of a composition containing either fibrin or ancrod or a combination of fibrin and ancrod is effective in minimizing scarring. Indeed, Edwardson et al. indicates that it is thrombin that is essential to the formation of the fibrin-based sealant.

In contrast, when ancrod is applied to a wound where blood is present, it will cleave the endogenous fibrinogen present in the blood to produce soluble non-cross-linked fibrin, fibrin that is more susceptible to plasmin degradation than thrombin generated fibrin and therefore, more readily cleared from the site.

10. I further declare that all statements of the foregoing Declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

17 October 2008
Date

Gregory J. Del Zoppo, M.D.